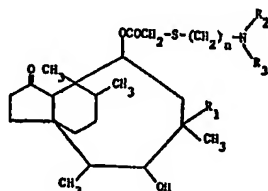


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**(54) Process for the Production of Pleuromutilin Derivatives**

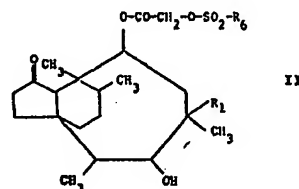
(57) The present invention provides a process for the production of compounds of formula I,



in which  
 n is 2, 3, 4 or 5  
 R<sub>1</sub> is ethyl or vinyl, and either  
 R<sub>2</sub> and R<sub>3</sub> are the same or different  
 and each signifies alkyl of 1 to 4  
 carbon atoms, or

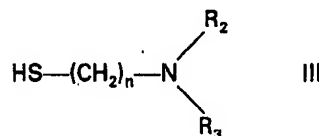
R<sub>2</sub> and R<sub>3</sub>, together with the  
 nitrogen atom to which they are  
 attached, form a heterocyclic ring  
 optionally containing a second hetero  
 moiety selected from oxygen, sulphur  
 or =N—R<sub>6</sub>, in which R<sub>6</sub> is alkyl of 1 to  
 4 carbon atoms,

or an acid addition salt form  
 thereof, comprising reacting a  
 compound of formula II,



in which

R<sub>1</sub> is as defined above, and  
 R<sub>6</sub> is alkyl of 1 to 4 carbon atoms or  
 phenyl, unsubstituted or substituted  
 by alkyl of 1 to 4 carbon atoms,  
 with a compound of formula III,



In which n, R<sub>2</sub> and R<sub>3</sub> are as defined  
 above, characterised in that the  
 reaction is effected in the presence of  
 a phase transfer catalyst, and, where  
 required, converting a resulting free  
 base form of the compounds of  
 formula I into an acid addition salt  
 form, or *vice versa*.

The compounds of formula I are  
 indicated for use as antibiotics having  
 an antibacterial effect and are also  
 indicated for use as prophylactic  
 additives for animal feeding stuffs and  
 animal drinking water.

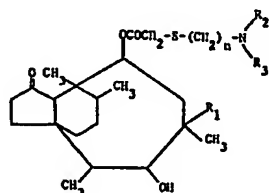
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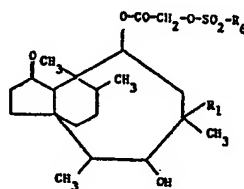
# SPECIFICATION Improvements In or Relating to Organic Compounds

This invention concerns pleuromutilin derivatives.

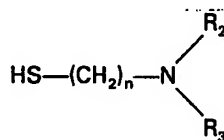
More particularly, this invention provides a process for the production of compounds of formula I,



- 10 in which  
n is 2, 3, 4 or 5,  
R<sub>1</sub> is ethyl or vinyl,  
and either  
R<sub>2</sub> and R<sub>3</sub> are the same or different and each  
15 signifies alkyl of 1 to 4 carbon atoms,  
or  
R<sub>2</sub> and R<sub>3</sub>, together with the nitrogen atom to  
which they are attached, form a heterocyclic ring  
optionally containing a second hetero moiety  
20 selected from oxygen, sulphur or =N-R<sub>5</sub>, in which  
R<sub>5</sub> is alkyl of 1 to 4 carbon atoms,  
or an acid addition salt form thereof, comprising  
reacting a compound of formula II,



- 25 in which  
R<sub>1</sub> is as defined above,  
and  
R<sub>6</sub> is alkyl of 1 to 4 carbon atoms or phenyl,  
unsubstituted or substituted by alkyl of 1 to 4  
30 carbon atoms,  
with a compound of formula III,



- 35 In which n, R<sub>2</sub> and R<sub>3</sub> are as defined above,  
characterised in that the reaction is effected in the  
presence of a phase transfer catalyst.

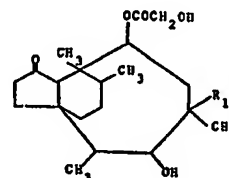
- The process is suitably effected by addition of a  
solution of the compound of formula II in an inert,  
water-immiscible solvent, for example an  
aromatic solvent, such as toluene, to an aqueous  
40 solution of the compound of formula III, which is  
suitably in the form of an acid addition salt, for  
example in hydrochloride salt form. The reaction is  
conveniently effected at a temperature of from  
25° to 70°C. Suitable phase transfer catalysts

- 45 are conventional such catalysts, including benzyl  
tributylammonium bromide and  
tetrabutylammonium bromide. The catalyst is  
conveniently present in catalytic amounts, for  
example 1 to 2 mol %. The reaction mixture is  
50 then suitably made alkaline, for example by  
addition of aqueous alkali metal hydroxide, e.g.  
sodium hydroxide solution.

The resulting compounds of formula I may be  
isolated and purified in conventional manner.

- 55 Where required, free base forms thereof may be  
converted into acid addition salt forms in  
conventional manner, and *vice versa*. Suitable salt  
forms include the hydrochloride and hydrogen  
fumarate.

- 60 The compounds of formula II are known and  
may be produced by reacting a compound of  
formula IV,



- in which  
65 R<sub>1</sub> is as defined above,  
with a compound of formula V,



V

in which

A is the acid radical of a reactive ester.

- 70 The reaction may be effected in known  
manner, for example as described in Example 1  
hereinafter. "A" suitably signifies chlorine or  
bromine. The resulting compounds of formula II  
may, if desired, be isolated and purified using  
75 conventional techniques but are preferably  
employed without isolation in the subsequent  
step of producing compounds I.

The compounds of formula I are known  
antibiotics with anti-bacterial activity and may, for  
80 example, be used for treating (prophylaxis or  
therapy) micro-organism infections in domestic  
animals, e.g. pigs and poultry.

- The preferred compounds of formula I are  
those in which n is 2 or 3, in particular 2. R<sub>1</sub> may  
be ethyl but is preferably vinyl. R<sub>2</sub> and R<sub>3</sub> are  
85 preferably each alkyl of 1 to 4, in particular 1 to 3,  
carbon atoms, more particularly 2 carbon atoms.  
They may, however, as indicated, also form a  
heterocyclic ring together with the nitrogen atom  
to which they are attached. Such ring suitably  
90 contains a second moiety. When the ring contains  
6 ring members, this is preferably para to the  
nitrogen atom. The second hetero moiety is  
preferably oxygen or, more preferably, =N-R<sub>5</sub>. R<sub>5</sub>  
95 is preferably alkyl of 1 to 2 carbon atoms.

- The process of the invention is generally  
known. It has, however, been found that by  
carrying out the process in the presence of a  
phase transfer catalyst, not only are the yields  
100 improved somewhat but also the need to isolate  
the starting material of formula II can be

eliminated. In addition, the process may be effected in solvents such as toluene, which may more easily and completely be regenerated thus leading to decreased environmental problems.

- 5 Finally, the required reaction time is diminished and working up is simplified.

The following Examples illustrate the invention.

#### Example 1

- 10 **14-Desoxy-14-[(2-diethylaminoethyl)-mercapto-acetoxy]mutilin**  
250 g of 14-desoxy-14-hydroxyacetoxy mutilin are suspended in a mixture of 900 ml of toluene and 300 ml of 15% aqueous sodium hydroxide solution, at room temperature. The mixture is heated to about 60°C and mixed, with stirring, with a solution of 138 g of *p*-toluenesulphonyl chloride in 350 ml of toluene. The mixture is stirred for 1½ hours at 60°C and the still warm aqueous phase is separated off. The toluene phase containing 14-desoxy-14-tosyloxyacetoxy mutilin is mixed with 112 g of diethylaminoethanethiol hydrochloride, 175 ml of water and 3.5 g of benzyltributylammonium bromide and 165 ml of concentrated caustic soda are added, with stirring to the resulting mixture at 60°C. The mixture is stirred for 2 hours at 60°C, the aqueous phase is then separated off and the toluene phase is extracted with dilute sulphuric acid. The H<sub>2</sub>SO<sub>4</sub> extract is made alkaline (pH=12) with 2 N caustic soda and precipitated heading compound extracted with toluene. The toluene solution is evaporated to obtain the heading compound in the form of a yellow oil.

- 35 The resulting free base may be treated with fumaric acid in known manner to obtain the hydrogen fumarate salt form, m.p. 148—149°C.

#### Example 2

- 40 In manner analogous to Example 1 and employing appropriate starting materials in approximately equivalent amounts, the following compounds may be obtained:—

- 14-desoxy-14-[(2-morpholinoethyl)mercapto-acetoxy]mutilin hydrochloride, softening point 70°C,  
45 14-desoxy-14-[(2-diisopropylaminoethyl)-mercaptoacetoxy]-mutilin hydrochloride,  
14-desoxy-14-[(di-*n*-butylaminoethyl)-mercaptoacetoxy]-mutilin hydrochloride, softening point 85—90°C  
50 14-desoxy-14-[2-(4-methyl)piperazinoethyl)-mercaptoacetoxy]mutilin dihydrochloride, m.p. 185—188°C,  
14-desoxy-14-[(2-dimethylaminoethyl)-mercaptoacetoxy]-dihydromutillin, trimethyl ammonium iodide, softening point 123—128°C,  
55 14-desoxy-14-[3-(di-*n*-butylaminopropyl)-mercaptoacetoxy]-mutilin hydrochloride, softening point 45—48°C,  
14-desoxy-14-[3-(di-*n*-butylaminopropyl)-mercaptoacetoxy]-dihydromutillin hydrochloride, softening point ~90°C,  
60 14-desoxy-14-[(2-thiomorpholinoethyl)-mercaptoacetoxy]-mutilin hydrochloride,

softening point 120—125°C, and

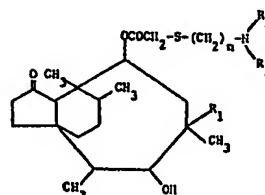
- 65 14-desoxy-14-[2-(4-methylpiperazino)ethyl-mercaptoacetoxy]-dihydromutillin, dihydrochloride m.p. 220°—225°C.

#### Example 3

- 70 The procedure of Examples 1 and 2 may be effected in analogous manner but employing tetrabutylammonium bromide in place of benzyltributylammonium bromide, in an approximately equivalent amount, to obtain the compounds indicated.

#### 75 Claims

1. A process for the production of compounds of formula I,



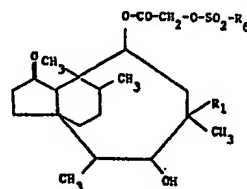
In which

- 80 *n* is 2, 3, 4 or 5,  
*R*<sub>1</sub> is ethyl or vinyl,  
and either

*R*<sub>2</sub> and *R*<sub>3</sub> are the same or different and each signifies alkyl of 1 to 4 carbon atoms,

- 85 or

*R*<sub>2</sub> and *R*<sub>3</sub>, together with the nitrogen atom to which they are attached, form a heterocyclic ring optionally containing a second hetero moiety selected from oxygen, sulphur or =N—*R*<sub>5</sub>, in which *R*<sub>5</sub> is alkyl of 1 to 4 carbon atoms, or an acid addition salt form thereof, comprising reacting a compound of formula II,

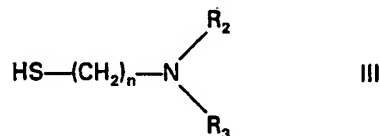


in which

- 95 *R*<sub>1</sub> is as defined above,  
and

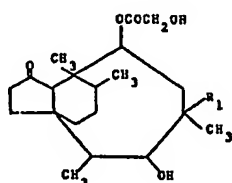
*R*<sub>2</sub> is alkyl of 1 to 4 carbon atoms or phenyl, unsubstituted or substituted by alkyl of 1 to 4 carbon atoms,

- 100 with a compound of formula III,



- in which *n*, *R*<sub>2</sub> and *R*<sub>3</sub> are as defined above, characterised in that the reaction is effected in the presence of a phase transfer catalyst, and, where required, converting a resulting free base form of the compounds of formula I into an acid addition salt form, or *vice versa*.

2. A process according to Claim 1, in which the compound of formula II is produced by reacting a compound of formula IV,



IV

5 in which

$R_1$  is as defined in Claim 1, with a compound of formula V,



V

in which

10 A is the acid radical of a reactive ester.

3. A process according to Claim 1, in which the phase transfer catalyst is benzyltributylammonium bromide or tetrabutylammonium bromide.

15 4. A process according to Claim 1, in which the reaction is effected by mixing a solution of the

compound of formula II, in an inert, water-immiscible organic solvent with an aqueous solution of the compound of formula III or mixture of the compound of formula III with water.

20

5. A process according to Claim 4, in which the inert water-immiscible organic solvent is toluene.

6. A process for the production of a compound of formula I, as defined in Claim 1, substantially as hereinbefore described with reference to any one of the Examples.

25

7. A compound of formula I, as defined in Claim 1, whenever produced by a process as claimed in any one of the preceding claims.

30

8. A process for the production of 14-desoxy-14-[(2-diethylaminoethyl)mercapto-acetoxy]-mutilin comprising reacting 14-desoxy-14-tosyloxy-acetoxymutlin with diethylaminoethanethiol hydrochloride under alkaline conditions and in the presence of a phase transfer catalyst.

35

9. 14-Desoxy-14-[(2-diethylaminoethyl)mercaptoacetoxy]mutlin whenever produced by the process of Claim 8.

40

10. The compound of Claim 9, in hydrogen fumarate salt form.